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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,996	05/24/2000	Mark T. Keating	408-916010US	4041

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	17

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,996	KEATING ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7-16-03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *5,15-21,25 and 40-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-14,22-24,26-39 and 48-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-16-03 has been entered.

Claims 1, 39, 48, 49 and 53 have been amended. Claims 1-59 are pending and claims 1-4, 6-14, 22-24, 26-39 and 48-59 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4, 6-14, 22-24, 26-39 and 48-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a tropoelastin or 7 repeats of the sequence of SEQ ID No. 1 (VGVAPG) or a method for preventing vascular restenosis by using said composition *in vitro* or via direct administration of said composition to a targeted site *in vivo*, does not reasonably provide enablement for a pharmaceutical composition comprising a polypeptide comprising an amino acid sequence at least 80% or 90% identical to SEQ ID No. 3, or comprising a peptide fragment including at least one hexameric sequence represented by SEQ ID No. 1 and a method for prophylaxis or treatment of a disorder having diminished capacity to regulate smooth muscle cell function, including

vascular stenosis, obstructive vascular disease, stenosis and restenosis, by delivering said pharmaceutical composition to a targeted site via any administration route *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-4, 6-14, 22-24 and 25-39 are directed to a pharmaceutical composition that provides an elastin-based composition comprising a polypeptide comprising an amino acid sequence at least 80% or 90% identical to SEQ ID No. 3, or a fragment including at least one hexameric sequence of SEQ ID No. 1, to a target site *in vivo*, wherein said composition has one or more biological activities of inhibiting proliferation, stimulating differentiation, or regulating migration of smooth muscle cells *in vivo* or binding to smooth muscle cells, and a method for prophylaxis or treatment of a disorder having diminished capacity to regulate smooth muscle cell function by delivering said pharmaceutical composition to a targeted site *in vivo*. Claims 6 and 26 specify said elastin-based composition comprises a recombinant tropoelastin. Claims 7-9 and 27 specify said elastin-based composition comprises a synthetic elastin peptide, such as two repeats or 6 repeats of VGVAPG. Claims 11 and 29 specify the composition comprises an elastin matrix produced from a blood vessel. Claims 12-14, 30 and 31 specify the composition is attached to a biocompatible support. Claim 33 specifies the delivery comprises intravascular delivery directly to a vascular site. Claim 34 specifies the disorder is atherosclerosis, restenosis, aneurysm, vascular bypass graft stenosis, dissection, or transplant arteropathy. Claims 36-38 specify the pharmaceutical composition is a tubular elastin-based composition as an artificial blood vessel for vascular bypass or coronary artery bypass grafting.

The claims read on using any polypeptide, derived from numerous organisms, comprising an amino acid sequence at least 80% or 90% identical to SEQ ID No. 3, or a fragment including at least one hexameric sequence of SEQ ID No. 1, in a pharmaceutical composition for prophylaxis or treatment of disorder having diminished capacity to regulate smooth muscle cell function. The specification discloses use of a human tropoelastin or 7 repeats of the sequence of SEQ ID No. 1 (VGVAPG) for preventing vascular restenosis *in vitro.* The claims encompass using various structural variants of SEQ ID No. 3 derived from numerous organisms or any polypeptide comprising SEQ ID NO. 1, which is a hexamer, to prevent or treat disorders having diminished capacity to regulate smooth muscle cell function in vivo. A polypeptide comprising an amino acid sequence that is at least 80% or 90% identical to SEQ ID No. 3 or a polypeptide comprising SEQ ID No. 1 could vary dramatically from the amino acid sequence of SEQ ID No. 3 or SEQ ID No. 1.

The term "pharmaceutical composition" implies therapeutic effects in vivo. The specification fails to provide adequate guidance and evidence that the claimed polypeptides would have biological activities as disclosed, such as inhibiting proliferation, stimulating differentiation, or regulating migration of smooth muscle cells *in vivo* or binding to smooth muscle cells in vivo or in vitro, such that said polypeptides would provide therapeutic effect in treating or preventing diseases or disorders in vivo. The specification also fails to provide information concerning structural feature except the disclosed 7 repeats of VGVAPG that contributes to the function of elastin or tropoelastin for preventing or treating disorders in vivo as set forth above. Although 7 repeats of VGVAPG has a function of preventing vascular restenosis, there is no evidence of record that indicates one or two repeats of VGVAPG or other number or VAVGPG repeats alone would have the same biological function as 7 repeats of VAVGPG *in vivo*. Raju et al., 1987 (J. Biol. Chem., Vol. 262(12): 5755-5762) reports that pentapeptide PGVGV repeat sequence is associated with a labile beta-spiral structure (beta-turn

repeat), and "This pentapeptide repeat occurs 11 times between residues 334 and 390...in bovine elastin and also in the corresponding sequence of pig elastin. However, in the corresponding sequence of chicken elastin, this pentapeptide repeat occurs only twice and is followed by a tripeptide repeat (PVG, 12 times; see Fig. 3). This would suggest that the labile beta-labile structure involving this pentapeptide repeat is not essential for the function of elastin" (e.g. p. 5761, right column). Different elastin or tropoelastin derived from different organisms can have different types of repeat that might contribute to the biological function of elastin or tropoelastin. It is unclear whether the VGVAPG repeat and how many VGVAPG repeat is the structural feature required for elastin or tropoelastin having the biological activities as set forth above.

Further, Tajima et al., 1997 (Archives of Dermatological Research, Vol. 289, No. 8, p. 489-492) reports that synthetic elastin peptide VPGVG stimulates the proliferation of chick vascular smooth muscle cells, which is contrary to the disclosed biological activity of inhibiting proliferation of smooth muscle cells of the claimed polypeptides. Tajima shows that both monomer and polymer of VGVAPG enhanced cell proliferation of fibroblast cells, however, both monomer and polymer of VPGVG do not (p. 489, left column, p. 490, left column). It is evident that a single amino acid difference could result in totally different biological activities of the synthetic peptides. Thus, one skilled in the art at the time of the invention would not known whether any fragment of a elastin or tropoelastin or variants of SEQ ID No. 3, i.e. human elastin, either occurs naturally or synthesized artificially, except the disclosed 7 repeats of VGVAPG would have the disclosed biological activities, such as inhibiting proliferation, simulating differentiation, or regulating migration of smooth muscle cells, so as to prevent or treat various disorders, such as atherosclerosis, restenosis, aneurysm, vascular bypass graft stenosis, dissection, or transplant arteropathy *in vivo*.

In addition, it was well known in the art that amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed

from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Polypeptides or peptides comprising at least one hexameric sequence of SEQ ID No. 1 encompasses adding unknown amino acid sequences to 5' and/or 3'end of SEQ ID No. 1 and those unknown sequence may affect or alter the biological function of SEQ ID No. 1. Since protein function is unpredictable from mere amino acid sequences, it would be unpredictable whether SEQ ID No. 1 alone or a polypeptide comprising SEQ ID No. 1 would have the claimed biological functions. In view of broad scope of numerous variants of SEQ ID No. 3 and peptide fragments comprising SEQ ID No. 1, the lack of detailed information regarding the structural and functional requirements for various elastins or tropoelastins having the biological activities as set forth above, and the unpredictability of polypeptide or peptide

function from mere amino acid sequence, it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

As discussed above, the phrase "pharmaceutical composition" implies therapeutic effects *in vivo*. The claims read on using the pharmaceutical composition to prevent or treat disorders as set forth above via various administration routes *in vivo*. The specification fails to provide adequate guidance and evidence that the claimed polypeptides could be used for prophylaxis or treatment of disease or disorders, such as atherosclerosis, restenosis, vascular bypass graft stenosis, transplant arteriopathy, aneurysm and dissection etc., so as to provide therapeutic effect in treating or preventing said diseases or disorders via various administration routes *in vivo*. It was known in the art that administration route of a pharmaceutical composition plays an important role in the efficiency of said composition *in vivo*. The type of administration route determines how the claimed elastin-based composition reaches its targeted site *in vivo*. The location of administration, the amount and stability of the polypeptides or peptides *in vivo*, and its compartmentalization within the cell are all important factors in determining whether sufficient polypeptides or peptides can reach their target site so as to provide therapeutic effects for preventing or treating diseases or disorders as set forth above *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the claims compositions are formulated in association with a biocompatible support and delivered to a target site and the claims are directed to particular routes of administration (amendment, p. 11). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection. Formulation in association with a biocompatible support only specifies the tool used for delivering the claimed

composition but fails to specify the administration routes. The claimed composition can be administered at one site remote to the target site and expect the claimed composition to reach the target site or can be administered directly to the target site. The claims still encompass various administration routes in vivo and the specification fails to provide sufficient enabling disclosure for the full scope of the invention claimed for the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection.

Applicants argue that the specification provide extensive guidance regarding making and ttesting of various elastin-based polypeptides and fragments and the reference cited by examiner was published far before the filing of the present invention and the art of protein making and testing have advanced since then. Applicants further argue that a considerable amount of experimentation is permissible and no undue experimentation is required for the present invention (amendment, p. 12, 13). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection. The cited references span about 25 years, Rudinger, 1976, Kaye et al., 1990, and Skolnick et al., 2000, and until now the art of protein function from mere amino acid sequence is still unpredictable. Although method of making polypeptides or peptides and method of testing protein function have progressed, protein or peptide function is still unpredictable from mere amino acid sequence as discussed above under 35 U.S.C. 112 first paragraph rejection, especially, Raju et al., 1987, and Tajima et al., 1997 show that pentapeptides can have totally different biological functions from that of SEQ ID No. 1. Therefore, one skilled in the art at the time of the invention would have to engaged in undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the specification does not necessarily provide working example and Senior et al. demonstrates that peptide VGVAPG has chemotractic activity in fibroblasts and monocytes and the specification shows activity of tropoelastin and tropoelastin fragment comprising 7 repeats of CGCAPG in smooth muscle cells. Applicants cite Dr. Dean Li's

declaration and argue that peptide VGVAPG can induce action polymerization in vascular smooth muscle cells and promote vascular smooth muscle cell chemotaxis in vitro (amendment, p. 14, 15). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection. Although the Senior reference teaches that peptide VGVAPG has chemotractic activity in fibroblasts and monocytes and Dr. Li's declaration shows the function peptide VGVAPG on smooth muscle cells in vitro, the claimed invention is directed to the use of a peptide or polypeptide comprising VGVAPG in vivo and its function on smooth muscle cells. In vitro environment differs dramatically from the in vivo environment and the *in vitro* data can not be extrapolated into success in *in vivo* environment. Further, the claims encompass using the claimed polypeptides or peptides to treat or prevent various diseases or disorders via various administration routes in vivo but the specification fails to provide sufficient enabling disclosure for those uses of the claimed polypeptides or peptides via various administration routes in vivo. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.